CHAPTER 1

Introduction

Dementia – Early and late onset

Dementia is an umbrella term used to describe a deterioration of cognitive functions and the occurrence of behavioral problems caused by various neurodegenerative diseases.[1] These cognitive and behavioral disturbances interfere with daily functioning and eventually lead to loss of independence. The prevalence of dementia rises exponentially with age, varying from 0.7 to 1.9% in the 60-64 years age group, up to 26.4 to 79.5% in the 90 plus age group.[2] Estimated was that in 2010 35.6 million people were suffering from dementia worldwide.[3] Because of the ageing population and increased life expectancies the number of people with dementia worldwide is estimated to increase to 115.4 million cases in 2050,[3] stressing the burden that dementia poses on health care and society in the nearby future.

Whereas most patients diagnosed with dementia have reached a particular age, a small subgroup of patients have the onset of symptoms already before the age of 65.[1] A so-called diagnosis of early-onset dementia (EOD) has a large impact on both patient and caregiver because of age specific problems. Patients, often at the height of their career, may lose their job because of the disease.[4] Also, a shift in roles within a family may occur, meaning that (relatively young) children need to take care of one of their parents.[4] Distress is high in caregivers of young patients, because of a double burden that arises due to performance of important social tasks, such as breadwinning and parenting, besides caregiving responsibilities.[5] The estimated prevalence of EOD varies from 54.0 per 100.000 in the 30-64 age group in the UK, to 42.3 per 100.000 in the 18-64 age group in Japan.[6,7] In the 60-65 age group approximately 1% of the general population is affected.[6] It is estimated that 15.000 patients are diagnosed with EOD in the Netherlands.[8] Diagnosing EOD is challenging, because EOD is caused by a heterogeneous group of diseases.[9] The most prevalent subtype of EOD is Alzheimer's disease (AD), which accounts for approximately one third of the cases, followed by vascular dementia (VaD) and frontotemporal dementia (FTD).[1] More rare subtypes of dementia, such as dementia with

lewy bodies (DLB), are relatively common at an early age, compared to at an older age.[6] Also, behavioral symptoms are sometimes misinterpreted as for instance a burnout, leading to a longer period between symptom onset and diagnosis in younger patients than in older patients.[10]

Characteristics of patients with EOD

Executive function (EF) disorders, besides language and behavioral problems are relatively common in early stages of EOD.[11] EF include functions like planning, set-shifting, and inhibition, which are crucial for a person's independency.[12] Patients with EOD suffer less from memory problems in early disease stages when compared to patients with late-onset dementia (LOD).[11] Besides cognitive and behavioral problems, disturbances in the rest-activity rhythm may occur. The rest-activity rhythm is one of the 24-h circadian cycles,[13] and is produced by a complex interaction of both endogenous, such as activity of the suprachiasmatic nuclei, and exogenous factors, such as the light-dark cylce.[13] The rest-activity rhythm is important, because a good sleep is recuperative. Many studies focus on rest-activity rhythm disturbances in elderly people and patients with LOD,[14] because the rest-activity rhythm is related to caregiver distress and institutionalization.[15,16] Nonetheless, there has only been one study that explored potential differences in the rest-activity rhythm between patients with EOD as compared to patients with LOD. Interestingly, the outcomes of this study suggested an association between age of onset and the rest-activity rhythm, indicating that younger patients were more likely to have an instable rest-activity rhythm over days.[17] Given that disturbances in the rest-activity rhythm may increase caregiver burden,[16] particularly in caregivers of EOD patients whose distress levels are already high,[5] more research focusing on the rest-activity rhythm in EOD is needed, to investigate the nature of possible rest-activity rhythm disturbances in these patients. Summarizing, the main characteristics seen in patients with EOD are EF dysfunction, language and behavioral problems. Besides, depressive symptoms and decreased quality

of life (QOL) may be present. When studies on depressive symptoms in EOD are combined, a large variation in point-prevalence emerges: 17-67%.[18–21] Depressive symptoms are, in turn, associated with a lower QOL in older persons with dementia.[22,23] Studies targeting QOL specifically in patients with EOD are scarce. No studies have compared wellbeing in patients with EOD to wellbeing in cognitively intact controls. More insight in wellbeing of patients with EOD may give opportunities for treatment options, such as patient education.

To conclude, despite the severe impact of EOD on both patients and caregivers due to age specific problems, the EOD population is underrepresented in scientific literature. Given the differences between patients with EOD and LOD in the course of the disease concerning cognitive disorders,[11] reported findings of the rest-activity rhythm and wellbeing performed in patients with LOD cannot automatically be generalized to patients with EOD. More insight in these areas could contribute to specific care, tailored to the needs of patients with EOD, in the future.
With a cure for dementia being absent, studies investigating whether lifestyle factors that have been proven to be beneficial in patients with LOD may also benefit patients with EOD are highly relevant. One lifestyle factor that is increasingly recognized as being beneficial for cognition and dementia is physical activity. This lifestyle factor may be of particular interest to those that are still physically quite capable of performing physical activity, i.e. patients with EOD.[24]

Physical activity and cognition

EPIDEMIOLOGICAL STUDIES

In 1978 it was found that physically active older men performed faster on a reaction time task than physically inactive older man.[25] Since then, many studies have been performed studying the relationship between physical activity and cognition. *Cross-sectional studies* have shown that healthy older

people who report higher levels of physical activity perform better on cognitive tasks.[26] Using *prospective cohort studies* the relation between physical activity and the risk of developing dementia is studied. These studies have found that higher levels of self-reported physical activity reduces the risk of developing dementia later in life, compared to persons who reported physical inactivity.[27,28] For a review on studies focusing on physical activity and cognition using multiple study designs see Brown et al., 2013.[29] To study whether physical activity has a causal effect on cognition, intervention studies, preferably *randomized controlled trials* (RCT), are needed.

INTERVENTION STUDIES AND RCT DESIGNS

A landmark paper by Kramer and colleagues in 1999 presented the results of the first RCT, studying the effect of aerobic exercise on cognition in physically inactive older adults.[30] They showed that physically inactive adults who participated in a 6-month aerobic training, consisting of brisk walking, improved on EF tasks, in contrast to a group who performed stretching and toning exercises. Since then, the causal effect of physical activity on cognitive functioning, in particular EF, has been replicated in subgroups of healthy older adults,[31] patients with mild cognitive impairment (MCI),[32] and patients with LOD.[33] When looking at the entire body of literature of RCTs studying the causal effect of physical activity on cognitive functioning it appears that most intervention trials are performed in cognitively intact persons of middle and older age.[34] Unfortunately, the limited number of performed RCT studies that studied physical activity in dementia show mixed results,[34] which is mainly caused by heterogeneity in study designs and methodological issues.[35]

STUDIES IN PATIENTS WITH EOD

Neither cross-sectional nor intervention studies on physical activity focus on patients with EOD. Patients with EOD are however an interesting study population for this line of research for two reasons: 1) one of the main

characteristics of patients with EOD is executive dysfunction.[11] Especially EF have shown to be related to physical activity in RCTs with cognitively intact older persons and patients with MCI,[31,32] and 2) because of their young age, patients with EOD have better physical functioning than older patients,[24] and hence are more capable to perform physical activity. This gave rise to the aims of this dissertation. In the paragraphs below the aims and outline of this thesis are discussed.

Aims and outline of this thesis

The general aim of this thesis was to study the effect of different exercise interventions on cognitive functioning, (instrumental) activities of daily living, and quality of life, in patients with EOD, making use of an RCT design. Additionally, we posed cross-sectional research aims to study important aspects of the general research aim. The cross-sectional studies are described in Part I, the intervention study is described in Part II.

PART I

Cross-sectional studies in patients with early-onset dementia

First, in **chapter 2** we studied the relationship between the level of physical activity and EF. Second, in **chapter 3** we explored the rest-activity rhythm in patients with EOD. Actigraphy was used to assess the rest-activity rhythm. Measures of the rest-activity rhythm and measures of sleep were compared between patients with EOD and cognitively intact adults. Further, we explored which demographic, clinical, and lifestyle factors, such as the level of physical activity and medication use, contribute to disturbances in the rest-activity rhythm. Finally, we addressed emotional wellbeing in

chapter 4. We studied whether quality of life and depressive symptoms were the same for patients with EOD and cognitively intact adults. Subsequently, it was examined which demographic, clinical, and lifestyle factors, such as cardiovascular comorbidities and the level of physical activity, were associated with emotional wellbeing.

PART II

An exercise trial in patients with early-onset dementia

This part of the thesis focused on the effects of different exercise programs on cognitive functioning, (instrumental) activities of daily living, and quality of life in persons with EOD. In **chapter 5** we explored the theoretical background of this research aim in an exploratory review. We focused on brain regions that respond to exercise and that are affected in early-onset Alzheimer's Disease (EOAD), and neurobiological mechanisms that may underlie the effects of exercise on cognition. This review focused on EOAD in contrast to EOD, since it appeared that studies on EOD involved almost exclusively studies on EOAD. The study protocol of the intervention trial is presented in **chapter 6**. The design, randomization procedures and outcome measures are described, as well as the study size calculation and the proposed statistical analyses. The performance of the intervention trial proved to be difficult. After careful consideration it was decided not to analyze the intervention data. The specific challenges that we faced and the lessons learned during the intervention trial are discussed in **chapter 7**. Challenges during the recruitment, randomization, intervention, and data-collection phase are discussed.

Finally, in **chapter 8**, a summary and discussion of the main findings and conclusions is provided.

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